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School of Medicine

In partnership with

The Ohio State University College of Medicine

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Ohio University Heritage College of Osteopathic Medicine

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Statewide Webinar

Fatty Liver Disease: A Silent Epidemic

February 28, 2024

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Welcome

Michael W. Konstan, MD
Principal Investigator, Cardi-OH

Shari Bolen, MD, MPH
Co-Principal Investigator, Cardi-OH

Case Western Reserve University School of Medicine

About Cardi-OH

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Ohio Cardiovascular and Diabetes Health Collaborative

Founded in 2017, the mission of Cardi-OH is to improve cardiovascular and diabetes health outcomes and eliminate disparities in Ohio's Medicaid population.

WHO WE ARE: An initiative of health care professionals across Ohio's seven medical schools.

WHAT WE DO: Identify, produce, and disseminate evidence-based cardiovascular and diabetes best practices to primary care teams.

HOW WE DO IT: Best practices resources are available via an online library at Cardi-OH.org, including monthly newsletters, podcasts, webinars, and virtual clinics using the Project ECHO® virtual training model.

Learn more at Cardi-OH.org

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- The following speaker has a relevant financial interest or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of their presentation*:
  - Lanla F. Conteh, MD, MPH, MBA
- The following speakers have no relevant financial interest or affiliation with any organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of their presentation:
  - Shari Bolen, MD, MPH; Michael W. Konstan, MD; Amy Zack, MD
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Agenda

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Topics	Presenter(s)	Timing
Welcome and Overview	Michael W. Konstan, MD Shari Bolen, MD, MPH	5 mins.
Fatty Liver Disease: A Silent Epidemic	Lanla F. Conteh, MD, MPH, MBA	40 mins.
Audience Question and Answer	Amy Zack, MD (Moderator) Lanla F. Conteh, MD, MPH, MBA	10 mins.
Next Steps and Wrap Up	Shari Bolen, MD, MPH	5 mins.

Lanla F. Conteh, MD, MPH, MBA
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Fatty Liver Disease: A Silent Epidemic

Lanla F. Conteh, MD, MPH, MBA

Director, Hepatology

Program Director, Transplant Hepatology Fellowship

Division of Gastroenterology, Hepatology and Nutrition

Department of Internal Medicine

The Ohio State University

Objectives

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1. Screen and identify patients with MASLD and MASH.
2. Manage contributing risk factors to MASLD in patient care.
3. Describe current disparities in care in MASLD risk, assessment, and management.
4. Counsel stakeholders on current risks, treatment options, and prognosis.

Nomenclature Change

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- FLD → SLD
- NAFLD → MASLD
- NASH → MASH
- Met-ALD

New Nomenclature

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- "Nonalcoholic" → term that recognizes metabolic dysfunction as the underlying disease pathogenesis.
- "Fatty" liver perceived as stigmatizing.
- Now known as steatotic liver disease (SLD)
- Nonalcoholic fatty liver disease (NAFLD) → metabolic dysfunction-associated steatotic liver disease (MASLD).
- MASLD: hepatic steatosis + at least one of five cardiometabolic risk factors.
- NASH → metabolic dysfunction-associated steatohepatitis (MASH)

Allen AM, Pose E, Reddy KR, et al. Gastroenterology. 2024;166(2):P22-234.

New: Met-ALD

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- Metabolic dysfunction + alcohol-associated liver disease (Met-ALD).
- 140 grams/week and 210 grams/week for females and males respectively.
- Leads to higher risk of developing cirrhosis.
- Distinct diagnosis from ALD: defined and driven by harmful levels of alcohol consumption **alone.**

Balakrishnan M, Rehm, J. Hepatology. 2024;79(2):451-459.

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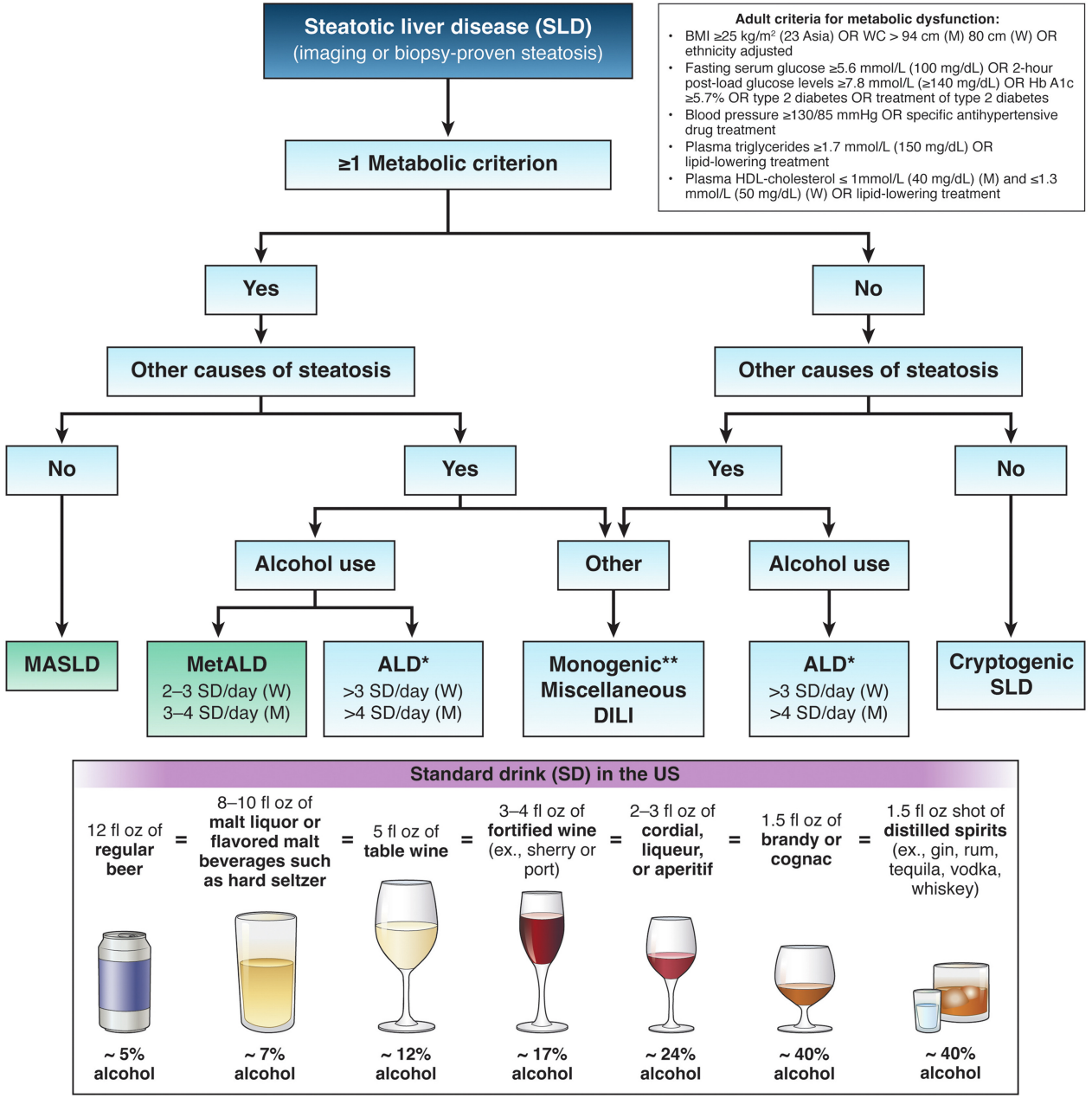

Each drink shown above represents one U.S. standard drink and has an equivalent amount (0.6 fluid ounces) of "pure" ethanol or approximately 14 grams of alcohol.

Allen AM, Pose E, Reddy KR, et al. Gastroenterology. 2024;166(2):P22-234.

Background: MASLD

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- Most widespread liver disease.
- Estimated prevalence of 38% in adults, 13% in children and adolescents.
- Increasingly important contributor to global morbidity and mortality.
- Liver disease accounts for > 2 million deaths/year and 4% of all deaths worldwide.
- Shares common metabolic risk factors with obesity, diabetes, and cardiovascular disease.
- Causes significant health, social, and economic consequences that impact at the individual, community, and population levels.

Younossi ZM, Golabi P, Paik J, et al, Hepatology. 2023;77(4):1335-1347.
Sweeny KF, Lee CK, Gastroenterol Hepatol (N Y), 2021;17(12):579-587.
Targher G, Tilg H, Byrne CD. Lancet Gastroenterol Hepatol. 2021;7(7):578-588.
Devarbhavi H, Asrani SK, Arab JP, et al. J Hepatol. 2023;79(2):516-537.

Significance

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- Patients are usually asymptomatic in early stages of disease.
- Will significantly impact public health; however, little foreplanning has been done.
- 2020 survey of 102 countries found that no country had a written strategy to address MASLD despite its burden.

Karlsen TH, Sheron N, Zelber-Sagi S, et al. Lancet. 2022;399(10319):61-116.
Lazarus JV, Mark HE, Villota-Rivas M, et al. J Hepatol. 2022;76(4):771-780.

Significance

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- Burden of MASLD expected to grow.
- Incidence of hepatic decompensation, hepatocellular carcinoma (HCC), and death related to MASLD cirrhosis also expected to increase 2- to 3-fold by 2030.
- MASLD-related cirrhosis is a leading indication for liver transplantation in women and those > 65 years of age.
- On par with alcohol as the leading indication overall.

Estes C, Razavi H, Loomba. R, et al. Hepatology. 2018;67(1):123-133.
Noureddin M, Vipani A, Bresee C, et al. Am J Gastroenterol. 2018;113(11):1649-1659.

Adverse Outcomes and Disease Stage

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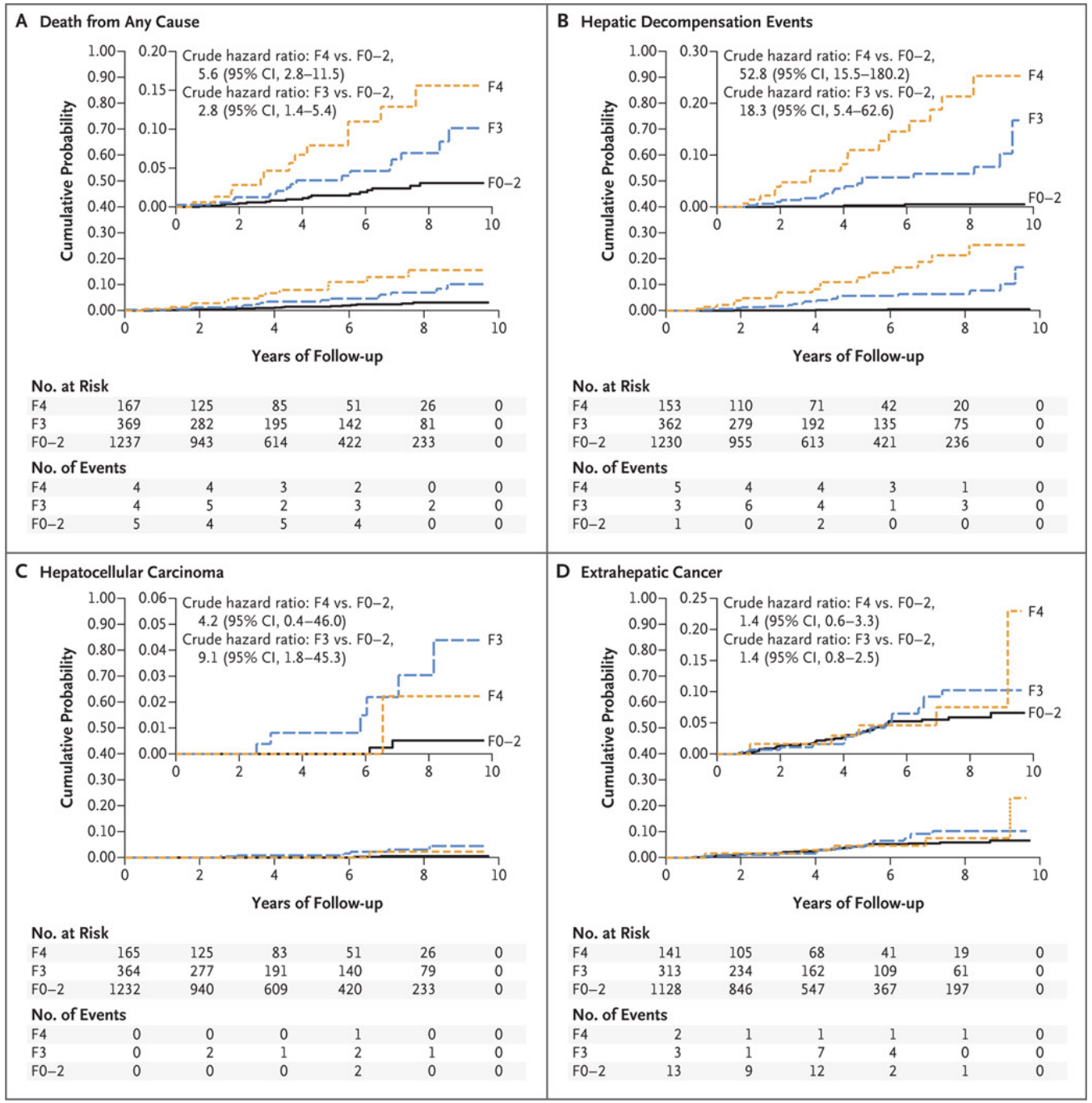
- Most common causes of death in patients with MASLD are cardiovascular disease (CVD) and nonhepatic malignancy, followed by liver disease.
- Amount of liver fibrosis has been strongly linked to the development of liver-related outcomes and death.
- Bridging fibrosis (F3) and cirrhosis (F4) are associated with greater risk of liver-related morbidity and mortality than earlier stages of fibrosis.
- Prospective study of 1773 patients.
  - All-cause mortality with F0–F2 was 0.32/100 person-years, compared with 0.89/100 person-years in those with F3 and 1.76/100 person-years in those with cirrhosis.

Sanyal AJ, Van Natta ML, Clark J, et al. N Engl J Med. 2021;385(17):1559-1569.



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Sanyal AJ, Van Natta ML, Clark J, et al. N Engl J Med. 2021;385(17):1559-1569.

Risk Factors for MASLD

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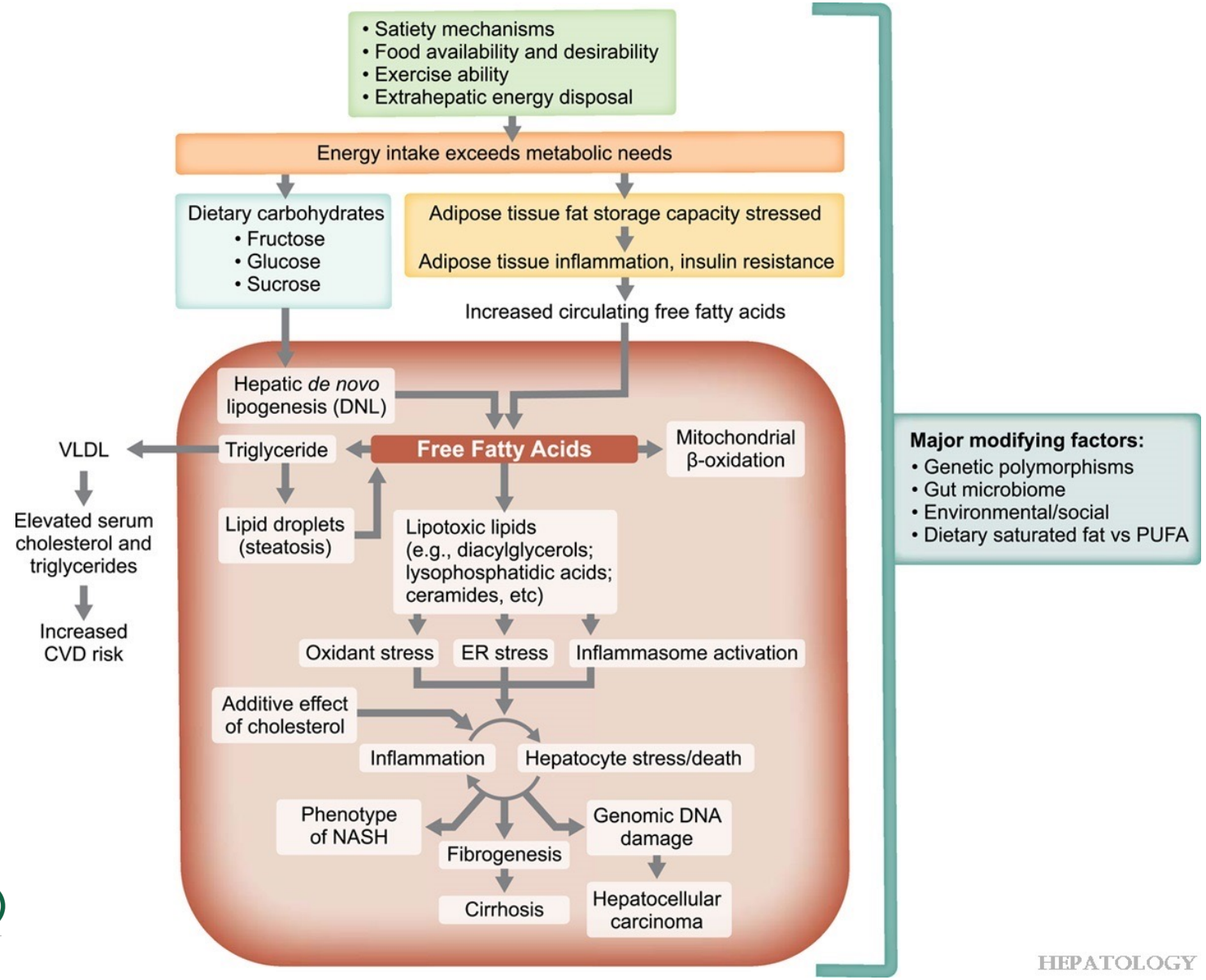
- Obesity
- Diabetes
- Dyslipidemia
- Hypertension



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AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HEPATOLOGY

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. Hepatology. 2023;77(5):1797-1835.

Obesity

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- Up to 30% of people with MASLD have MASH.
- Undergo fibrotic progression to cirrhosis over 20-30 years.
- Risk of developing MASLD increases 3-fold among adults with BMI of ≥ 25 kg/m^2 (≥ 23 kg/m^2 among Asian populations).
- Dose-dependent increases seen with every per unit increase in waist circumference and BMI.

Pang Q, Zhang J-Y, Song S-D, et al, World J Gastroenterol. 2015;21(5):1650-1662.
Balakrishnan M, Rehm J. Hepatology. 2024;79(2):451-459.

Obesity

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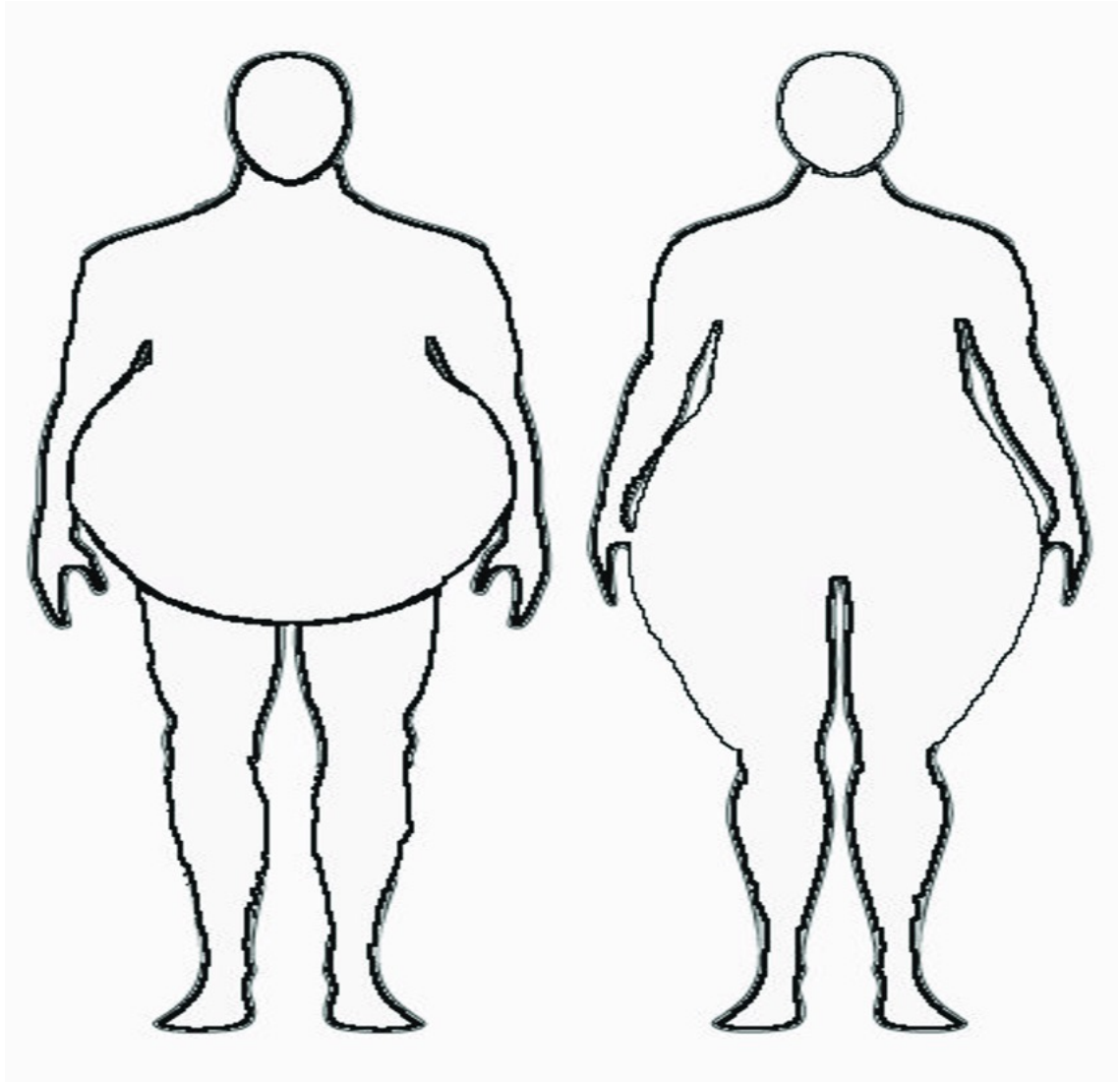
- Body fat distribution is an important determinant of the contributory role of obesity in MASLD.
- Android body fat distribution-increased truncal subcutaneous fat and visceral fat → higher risk of insulin resistance, CVD, and hepatic fibrosis, irrespective of BMI.
- Gynoid body fat distribution- increased subcutaneous body fat predominantly in the hips or buttocks → protective against MASLD.

van der Poorten D, Milner K-L, Hui J, et al. Hepatology. 2008;48(2)449-457.
Yu SJ, Kim W, et al. Medicine (Baltimore). 2015;94(48):e2159.



ANDROID GYNOID

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Type 2 Diabetes Mellitus (T2DM)

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- Most impactful risk factor for the development of MASLD, fibrosis progression, and HCC.
- Due to central pathogenic role that insulin resistance plays in the pathogenesis of both T2DM and MASLD.
- Patients with T2DM have a higher prevalence of MASLD (ranging from 30% to 75%) and a higher risk of developing MASH with fibrosis.
- Probability of advanced fibrosis increases with the duration of T2DM.

McPherson S, Hardy T, Henderson E, et al. J Hepatol. 2015;62(5):1148-1155.
Cusi K, Sanyal AJ, Zhang S, et al. Diabetes Obes Metab. 2017;19(11):1630-1634.

Type 2 Diabetes Mellitus

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- The relationship between MASLD and T2DM is bidirectional.
- The presence of MASLD is associated with a 2- to 5-fold risk of incident diabetes.
- Patients with MASLD should be screened for the presence of T2DM.
- Liver disease progression → insulin resistance and beta cell failure → challenge in managing DM.
- Prevalence is much lower in T1DM.
  - Closely related to coexistent metabolic risk factors (e.g., higher BMI).

McPherson S, Hardy T, Henderson E, et al. J Hepatol. 2015;62(5):1148-1155.
Cusi K, Sanyal AJ, Zhang S, et al. Diabetes Obes Metab. 2017;19(11):1630-1634.

Hypertension

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- Commonly associated with MASLD.
- Higher incidence of hypertension in those with MASLD.
- Presence of hypertension is additive to other metabolic comorbidities.
- Has been associated with fibrosis progression.

Sanyal A, Van Natta ML, Clark J, et al. N Engl J Med. 2021;385(17):1559-1569.

Dyslipidemia

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- Patients with MASLD are twice as likely to have plasma lipid abnormalities.
- High risk for coronary artery disease (CAD) despite the normalization of serum lipids and lipoproteins due to hepatic synthetic failure.
- Management should include the use of moderate-intensity to high-intensity statins as first-line therapy.
- Combination therapies of statins with other hypolipemic agents should be considered when monotherapy not effective.

Siddiqui MS, Fuchs M, Idowu MO, et al. Clin Gastroenterol Hepatol. 2015;13(5):1000-1008.
Patel SS, Nabi E, Guzman L, et al. Liver Transpl. 2018;24(3):333-342.

Dyslipidemia

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- Statins are safe in patients with MASLD across the disease spectrum.
- Lead to reduction in cardiovascular morbidity and mortality.
- In clinical practice, they are often underused.
- Statins are safe in the context of compensated cirrhosis.
- May have beneficial effects on future decompensation and HCC risk.

Bril F, Portillo Sanchez P, Lomonaco R, et al. J Clin Endocrinol Metab. 2017;102(8):2950-2961.
Kaplan DE, Serper MA, Mehta R, et al. Gastroenterology. 2019;156(6):1693-1706.
Blais P, Lin M, Kramer JR, et al. Dig Dis Sci. 2016;61(6):1714-1720.

Cardiovascular Disease (CVD)

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- CVD is an important cause of death in patients with MASLD.
- Strong association exists between MASLD and atherosclerotic cardiovascular disease, heart failure, and arrhythmias.
- Large prospectively studied observational cohort.
  - The incidence of cardiac events was the same across all fibrosis stages.
- Optimizing the management of CVD risk factors is critical to improving outcomes in patients with MASLD.
- Aggressively treat comorbid conditions such as hypertension, dyslipidemia, and hyperglycemia.
- Promote smoking cessation.

Loomba R, Schork N Chen C-H, et al. Gastroenterology. 2015;149(7):1784-1793.
Stepanova M, Younossi ZM. Clin Gastroenterol Hepatol. 2012;10(6):646-650.
Ekstedt M, Hagstrom H, Nasr P, et al. Hepatology. 2015;61(5):1547-1554.

Associations Between NASH and Fibrosis State at Enrollment With Mortality and Incident Non-Fatal Outcomes in Adults With Biopsy-Confirmed NAFLD

	NASH and Stage F3-4 fibrosis with decompensation		NASH and Stage F3-4 fibrosis without decompensation		NASH and Stage F-2 fibrosis		NAFLD, no NASH and Stage F0-2 fibrosis		NASH & F3-4 w/ decomp vs. NAFLD, No NASH & F0-2 HR* (95% CI)	NASH & F3-4 w/o decomp vs. NAFLD, No NASH & F0-2 HR* (95% CI)	NASH & F0-2 vs. NAFLD, no NASH & F0-2 HR* (95% CI)
	Rate /100 PY	# evt / # at risk	Rate /100 PY	# evt / # at risk	Rate /100 PY	# evt / # at risk	Rate /100 PY	# evt / # at risk			
All-cause mortality	11.76	9/19	0.82	20/517	0.31	12/827	0.32	6/410	17.2 (5.2, 56.6)	1.6 (0.6, 4.2)	0.9 (0.3, 2.4)
Liver-related mortality	5.22	4/19	0.24	6/517	0.05	2/827	0.00	0/410	‡	‡	‡
Liver-related											
Decompensation											
Variceal hemorrhage	2.13	1/12	0.21	5/513	0.00	0/826	0.00	0/406	‡	‡	‡
Ascites	0.00	0/5	0.71	17/513	0.05	2/824	0.00	0/405	‡	‡	‡
Encephalopathy	15.98	6/12	0.97	23/513	0.03	1/826	0.00	0/406	‡	‡	‡
Any hepatic decompensation event‡	--	0/0	1.45	34/515	0.08	3/824	0.00	0/406	‡	‡	‡
Hepatocellular carcinoma	0.00	0/18	0.29	7/511	0.05	2/826	0.00	0/406	‡	‡	‡
MELD† ≥ 15	9.89	5/17	1.10	26/506	0.54	20/816	0.65	12/405	13.8 (4.6, 41.0)	1.2 (0.6, 2.6)	0.7 (0.4, 1.5)
Cardiovascular											
Coronary artery disease†	0.00	0/15	0.92	20/469	0.95	34/789	0.51	9/394	‡	1.3 (0.5, 3.1)	1.7 (0.8, 3.7)
Cerebrovascular disease†	1.49	1/18	0.59	14/508	0.35	13/816	0.22	4/403	2.5 (0.1, 44.6)	1.8 (0.5, 6.0)	1.4 (0.4, 4.8)
Hypertension	6.07	1/5	12.93	66/162	7.63	93/320	4.89	42/208	0.9 (0.1, 7.7)	2.0 (1.3, 3.0)	1.5 (1.0, 2.2)
Renal Function¶											
eGFR < 60	6.70	4/17	3.30	69/473	2.32	80/782	1.87	32/388	1.4 (0.4, 5.1)	1.2 (0.8, 1.8)	1.1 (0.7, 1.6)
eGFR decline > 40%	1.38	1/18	1.78	42/514	1.07	40/824	0.76	14/405	0.7 (0.1, 6.5)	1.4 (0.8, 2.7)	1.2 (0.6, 2.1)
Other Co-morbidities											
Extrahepatic cancer	1.73	1/16	1.00	20/438	0.71	24/751	0.77	13/377	1.5 (0.2, 14.4)	1.3 (0.6, 2.6)	0.9 (0.5, 1.8)

Sanyal AJ, Van Natta ML, Clark J, et al. N Engl J Med. 2021;385(17):1559-1569.

Summary: MASLD Co-Morbidities

- Patients with diabetes are at higher risk for MASH and advanced fibrosis and should be screened.
- Patients with MASLD should be screened for the presence of T2DM.
- Statins are safe and recommended for CVD risk reduction in patients with MASLD across the disease spectrum.
- Death from nonhepatic malignancies is a common cause.
- Adherence to age-appropriate cancer screening has the potential to improve survival.

Role of Alcohol

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- Alcohol use is an important contributor to MASLD progression.
- Should be quantified in all patients.
- Moderate alcohol use increases the probability of advanced fibrosis particularly in patients with obesity or T2DM.
- Obesity and alcohol synergistically increase the risk of liver injury, cirrhosis, HCC, and death.
- Heavy alcohol consumption should be avoided in patients with MASLD.
- There is substantial variability in individual susceptibility to alcohol-induced liver injury.

Blomdahl J, Nasr P, Ekstedt M, Kechagias S. Metabolism. 2021;115:154439.
Chang Y, Ryu S, Kim Y, et al. Hepatology. 2020;71(3):861-873.

Alcohol Use Guidance

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- Patients with MASLD should have alcohol intake assessed on a regular basis.
- Patients with clinically significant hepatic fibrosis (≥ F2) should abstain from alcohol use completely.
- Abstinence may lower the risks of fibrosis progression and hepatic and extrahepatic malignancies in patients with MASLD.

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Screening

Screening for Presence of Clinically Significant Fibrosis

- Targeted screening of populations at increased risk for advanced liver disease is advised.
- Identify and manage those with clinically significant fibrosis (stage ≥ F2).
- Screening high-risk populations: T2DM, obesity with metabolic complications, a family history of cirrhosis, or significant alcohol use.
- May identify those with asymptomatic but clinically significant fibrosis.
- Early identification allows for interventions that may prevent future hepatic complications.

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS et al. Hepatology. 2023;77(5):1797-1835.

Screening for Presence of Clinically Significant Fibrosis

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Screening recommended	Prevalence of advanced fibrosis
T2DM	6% – 19%
Medically complicated obesity	4% – 33%
NAFLD in context of moderate alcohol use	17%
First-degree relative of a patient with cirrhosis due to NAFLD/NASH	18%

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS et al. Hepatology. 2023;77(5):1797-1835.

MASLD in Primary Care Practice

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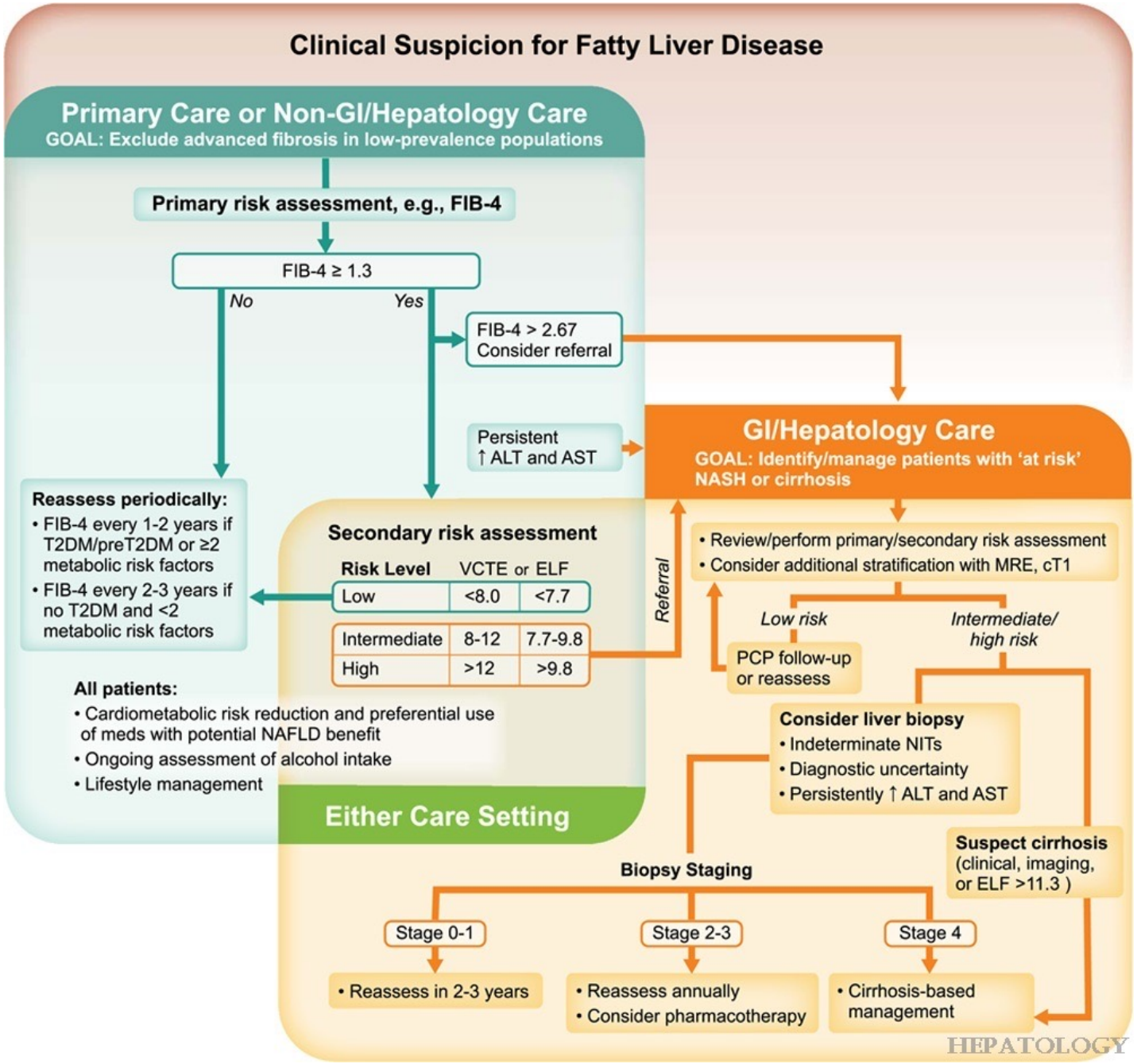
- Patients suspected to have MASLD should undergo primary risk assessment.
- Objective is to identify patients who are not likely to have advanced fibrosis [low risk, e.g., fibrosis-4 index (FIB-4) < 1.3].
- Patients in low-risk categories can be managed in primary care.
- Patients with ≥ 2 metabolic risk factors should undergo more frequent risk assessment with FIB-4 every 1–2 years.

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS et al. Hepatology. 2023;77(5):1797-1835.



Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. Hepatology. 2023;77(5):1797-1835.

Summary: Screening

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- General population-based screening for MASLD is not advised.
- All patients with hepatic steatosis or clinically suspected MASLD should undergo primary risk assessment with FIB-4.
- In patients with pre-DM, T2DM, or 2 or more metabolic risk factors, primary risk assessment with FIB-4 should be repeated every 1–2 years.
- First-degree relatives of patients with MASH cirrhosis should be counseled regarding their increased individual risk and offered screening.
- Patients with suspected advanced MASH or discordant non-invasive testing (NIT) should be referred to a specialist for evaluation.
- Aminotransferase levels are frequently normal in patients with advanced liver disease due to MASH.

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS et al. Hepatology. 2023;77(5):1797-1835.

Initial Evaluation of Patient with MASLD

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History	Weight history; medical comorbidities; recent and current medications; family history of T2DM, NAFLD, or cirrhosis; screening for OSA; alcohol use, including amount, pattern of use, and duration.
Physical examination	Body fat distribution (e.g., android vs. gynoid, lipodystrophic), features of insulin resistance (e.g., dorsal-cervical fat pad, acanthosis nigricans), features of advanced liver disease (e.g., firm liver, splenomegaly, prominent abdominal veins, ascites, gynecomastia, spider angiomata, palmar erythema).
Laboratory tests	Hepatic panel, CBC with platelets, fasting plasma glucose and glycated hemoglobin (A1C), fasting lipid profile, creatinine and urine microalbumin or protein to creatinine ratio, hepatitis C if not previously screened. Consider as appropriate other causes of steatosis/steatohepatitis. Additional evaluation if elevated liver chemistries present: autoimmune serologies, transferrin saturation, ceruloplasmin, alpha-1 antitrypsin genotype, or phenotype.

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Assessing Disease Stage- Non-Invasive Testing (NIT)

Biomarkers/NIT for Diagnosis and Assessment of MASLD

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- Liver biopsy assessment remains the gold standard for the grading and staging of MASLD/MASH.
- Has limitations related to risk, cost, and resource utilization.
- Liver biopsies for grading and staging of MASLD/MASH should be reserved for specific clinical scenarios.
- Noninvasive biomarkers are emerging as valuable tools for predicting adverse liver-related outcomes.

Estimation of Liver Fibrosis in Patients With Suspected or Confirmed NAFLD

- NIT derived from clinical variables can estimate of the presence of advanced fibrosis.
- Several have been developed (e.g., **FIB-4**, NAFLD Fibrosis Score, AST Platelet Ratio Index).
- **FIB-4 is the most validated.**
- FIB-4 is calculated based on age, ALT, AST, and platelet count.
- Outperforms other calculations in its ability to identify patients with a low probability of advanced fibrosis.
- A change in FIB-4 status category from low risk (< 1.3) to intermediate risk (1.3 – 2.67) to high risk (> 2.67) may be used to assess clinical progression.
- Recommended as a first-line assessment for general practitioners.

Sterling RK, Lissen E, Clumeck N, et al. Hepatology. 2006;43(6):1317-1325.
Unalp-Arida A Ruhl CE. Hepatology. 2017;66(1):84-95.

Parameters for Noninvasive Assessment of NAFLD According to Clinical Context of Use

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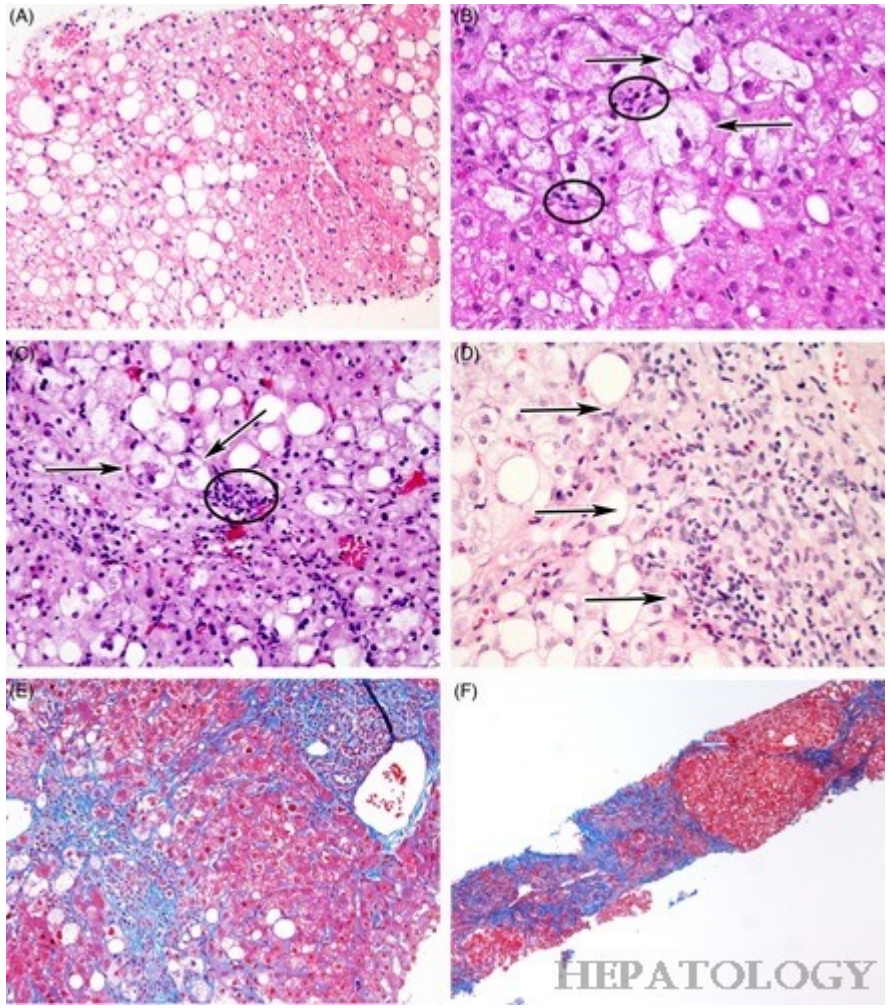
	Cut point		
Modality type	**Likely**	**Unlikely**	**Strengths/limitations, references/caveats**
Identification of hepatic steatosis			
Imaging			
Ultrasound	"Detected"	NA	Semiquantitative assessment: mild/moderate/severe; low sensitivity with less severe steatosis[322]; steatosis can have similar echo characteristics as advanced fibrosis
FibroScan: CAP	≥288 dB/min		Limited accuracy for quantification[323]
MRI-PDFF	≥5%	<5%	Most sensitive across spectrum of steatosis; accurate to assess dynamic change[324]
Identification of "at-risk" NASH			
FAST	≥0.67	<0.35	≤0.35 (sensitivity 90%), ≥0.67 (specificity 90%); in validation cohorts, the PPV of FAST ranged between 0.33 and 0.81[28,325]
MAST	≥0.242	≤0.165	0.242 (specificity 90%),[326] 0.165 (sensitivity 90%)[326]
MEFIB	FIB-4 ≥1.6 plus MRE ≥3.3 kPa	FIB-4 <1.6 plus MRE <3.3 kPa	Sequential approach identifies patients with at least stage 2 fibrosis with >90% PPV[327]
cT1	≥875 ms	<825 ms	Requires further validation[328]
Detection of advanced fibrosis			
Serum			
FIB-4	≥2.67	<1.3	No added cost[117,329,330]; not accurate in age <35 y and lower rule-out threshold among high-risk individuals who have high pretest probability
NFS	≥0.672	<−1.44	No added cost; not accurate in age <35 y, people with obesity and/or type 2 diabetes[117,329,330]
ELF	≥9.8	<7.7	Blood test sent to a reference laboratory[331]; cost
FIBROSpect II	≥17	<17	Blood test sent to a reference laboratory[332]; cost

Histology of NAFLD



Liver biopsy shows characteristic features of the spectrum of NAFLD:

A. Hepatic steatosis (typically zone 3) without ballooned hepatocytes or fibrosis.

B. Multiple ballooned hepatocytes with Mallory-Denk bodies (arrows) and mild lobular inflammation (circles).

C. Ballooned hepatocytes (arrows) with moderate lobular inflammation (circle).

D. Some cases of steatohepatitis may show significant portal inflammation and interface hepatitis (arrows).

E. Dense perisinusoidal and periportal fibrosis (blue stain), with a thin connecting fibrotic bridge.

F. Cirrhosis (nodule formation) due to steatohepatitis.

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. Hepatology. 2023;77(5):1797-1835.

Cirrhosis

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- Diagnosis of cirrhosis, determined by biopsy or noninvasively, is crucial.
- Changes clinical management.
- Patients with cirrhosis require biannual screening for HCC, screening for varices, and monitoring for signs or symptoms of decompensation.
- Among patients with cirrhosis, progression to clinical decompensation ranges from 3% to 20% per year.

Sanyal AJ, Van Natta ML, Clark J, et al. N Engl J Med. 2021;385(17):1559-1569.

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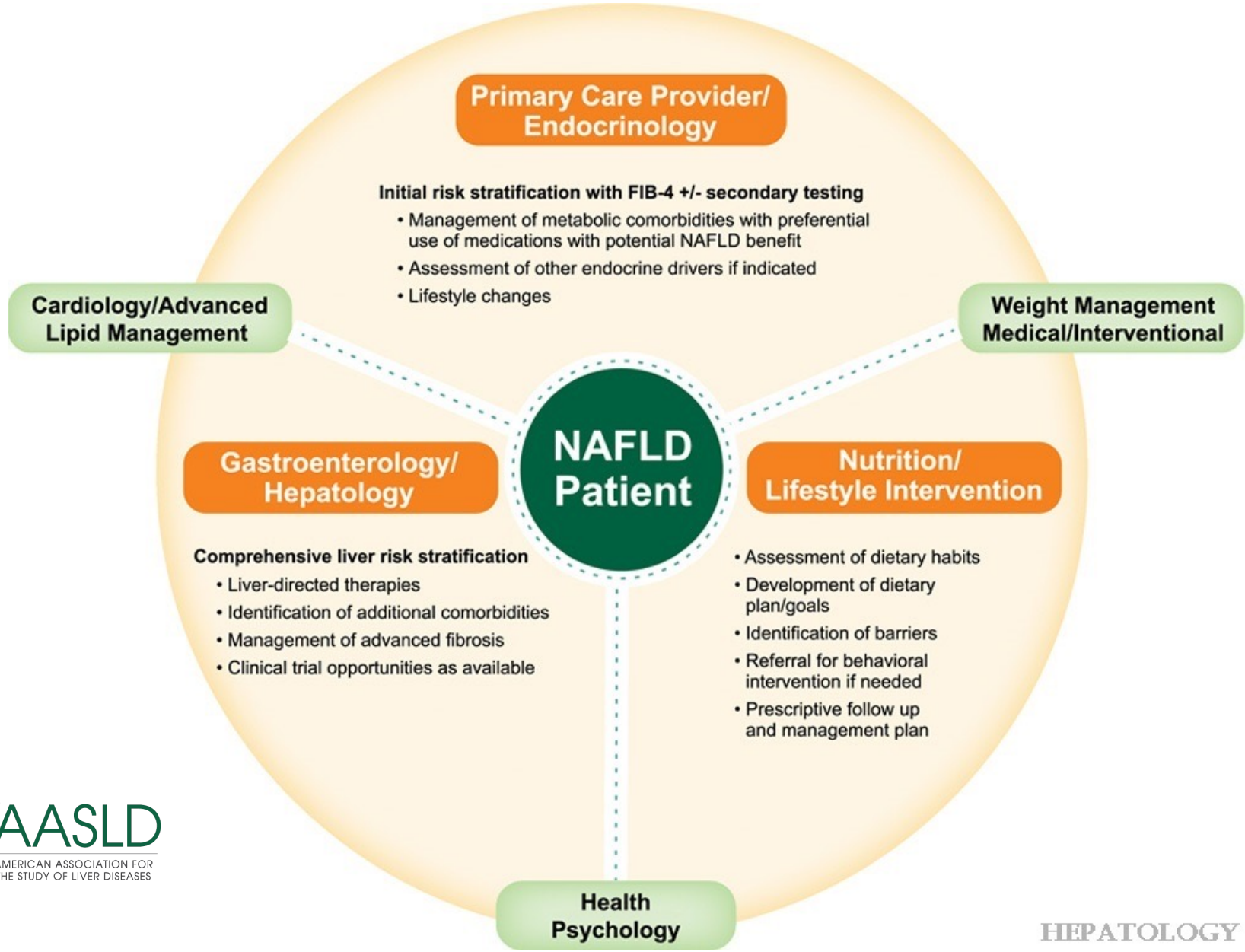
Treatment



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HEPATOLOGY

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. Hepatology. 2023;77(5):1797-1835.

Diet and Exercise

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- Healthy diet and regular exercise form the foundation of treatment for the vast majority with MASLD.

Semmler G, Datz C, Reiberger T, Trauner M. Liver Int. 2021;41(10):2249-2268.

Weight Loss

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- Even modest amounts of weight loss can be impactful, especially in those with milder disease.
- Weight loss of 3%-5% improves steatosis.
- Greater weight loss (> 10%) is generally required to improve MASH and fibrosis.
- Sustained weight loss reduces adipose tissue stress and improves peripheral insulin sensitivity.

Long MT, Noureddin M, Lim JK. Gastroenterology. 2022;163(3):764-774.
Koutoukidis DA, Astbury NM, Tudor KE, et al. JAMA Intern Med. 2019;179(9):1262-1271.

Diet

- Diet containing excess calories, excess saturated fats, refined carbohydrates, and sugar-sweetened beverages, is associated with obesity and MASLD.
- Excessive fructose consumption in particular increases the risk of MASLD, NASH, and advanced fibrosis independent of calorie intake.
- The Mediterranean diet is often recommended based on its associated improvement in cardiovascular health and reduction in liver fat.
- Coffee consumption, independent of caffeine content, may also be beneficial.

Vilar-Gomez E, Nephew LD, Vuppalanchi R, et al. Hepatology. 2022;75(6):1491-1506.
Ishimoto T, Lanaspa MA, Rivard CJ, et al. Hepatology. 2013;58(5):1632-1643.
Wijarnpreecha K, Thongprayoon C, Ungprasert P. Eur J Gastroenterol Hepatol. 2017;29(2):e8-e12.

Exercise

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- Exercise, independent of weight loss, has hepatic and cardiometabolic benefit.
- Should be routinely recommended and tailored to the patient's preferences and physical abilities.
- Studies demonstrate that regular moderate exercise at least 5 times/week can prevent or improve MASLD.

Sung K-C, Ryu S, Lee J-Y, et al. J Hepatol. 2016;65(4):791-797.
Semmler G, Datz C, Reinberger T, Trauner M. Liver Int. 2021;41(10):2249-2268.

Bariatric Surgery

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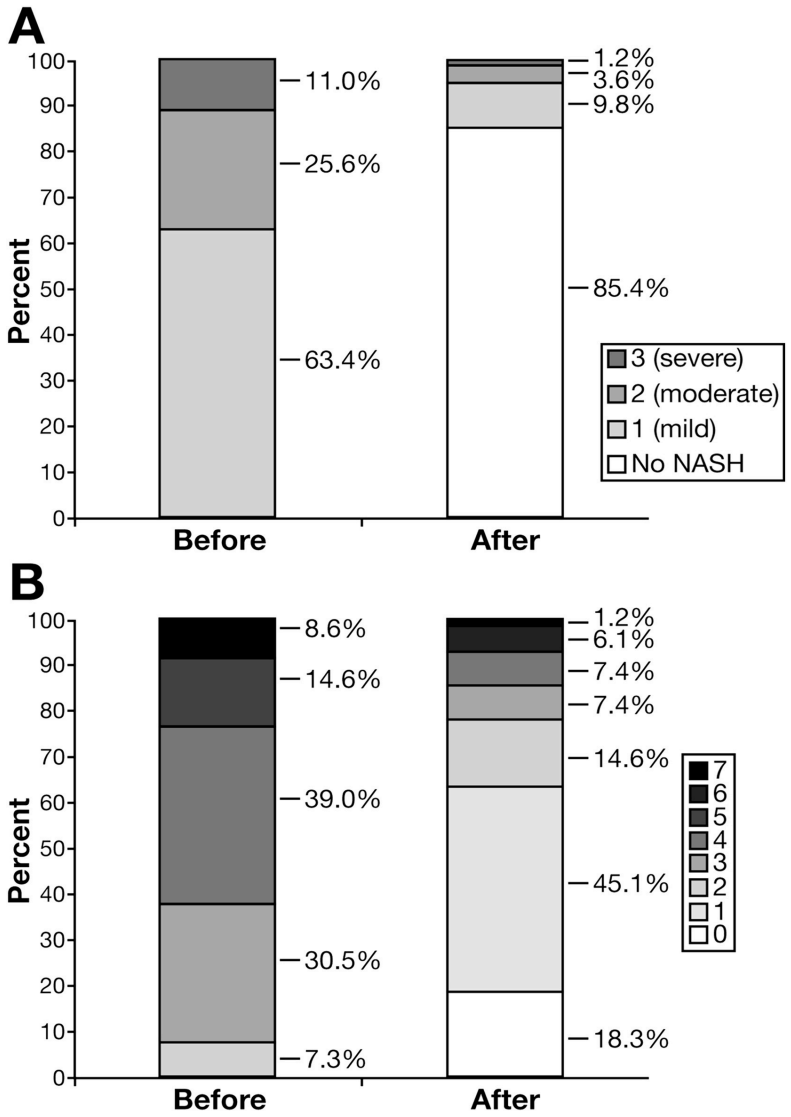
- Currently accepted criteria for bariatric surgery are BMI ≥ 40 kg/m^2 irrespective of metabolic comorbid disease or BMI ≥ 35 kg/m^2 with comorbidities (T2DM or pre-DM, uncontrolled hypertension, osteoarthritis of hip or knee).
- MASLD/MASH is increasingly accepted as a comorbid condition benefitting from bariatric surgery.
- The overwhelming majority of patients undergoing bariatric surgery have MASLD.
- Bariatric surgery can resolve NASH, improve hepatic fibrosis, induce sustained weight loss of up to 30%, cure diabetes, and decrease all-cause morbidity and mortality.
- Resolution of MASH without worsening of fibrosis occurred in 80% of patients 1 year following bariatric surgery which was maintained at 5 years.
- Failure to achieve substantial weight loss following bariatric surgery is associated with persistent MASH.
- Endoscopic bariatric and metabolic surgery procedures are promising less-invasive options.

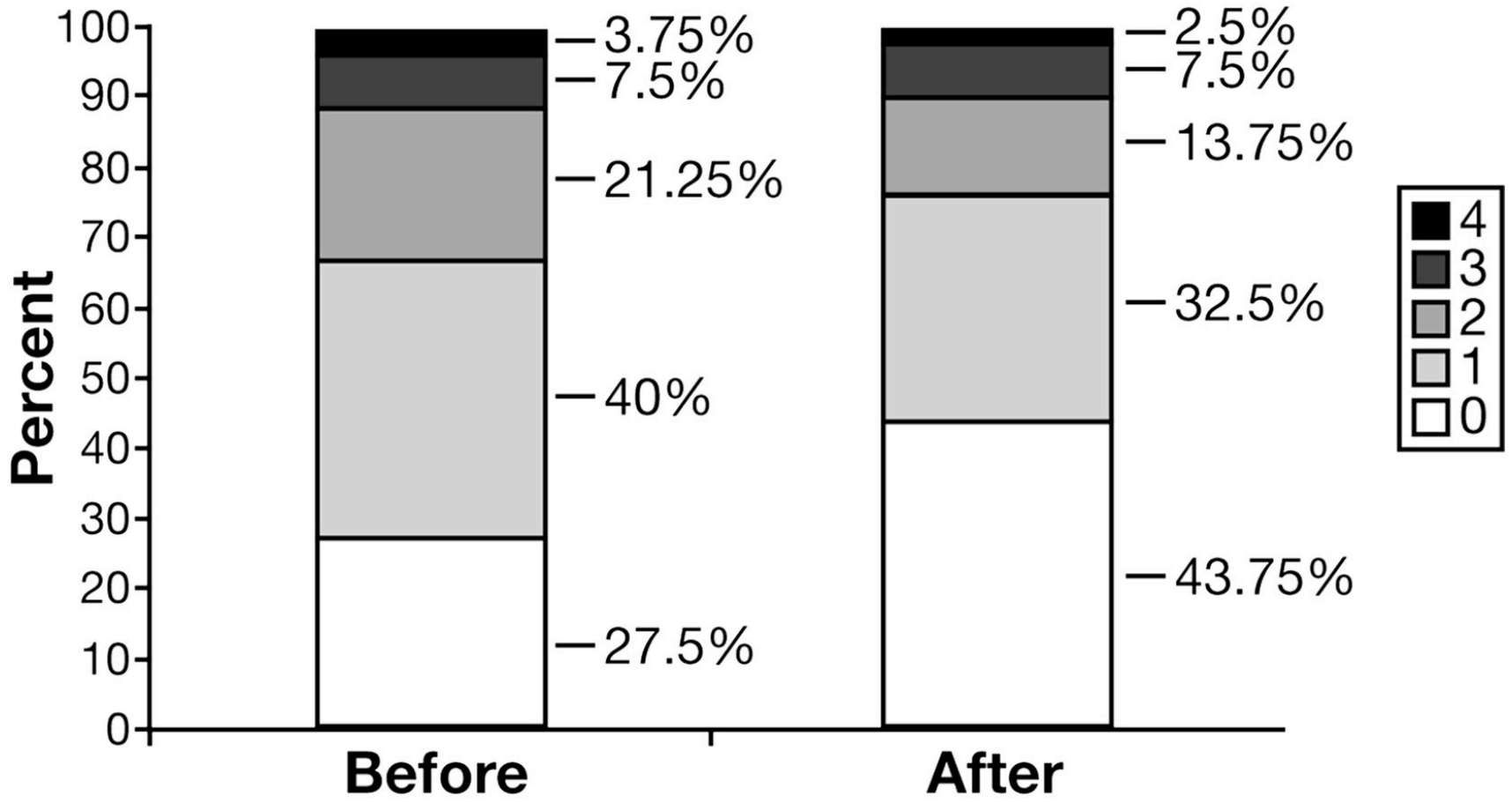
Lassailly G, Caiazzo R, Buob D, et al. Gastroenterology. 2015;149(2):379-388.
Lee Y, Doumouras AG, Yu J, et al. Clin Gastroenterol Hepatol. 2019;17(6):1040-1060.
Lassailly G, Caiazzo R, Ntandja-Wandji L-C, et al. Gastroenterology. 2020;159(4):1290-1301.
Jirapinyo P, McCarty TR, Dolan RD, et al. Clin Gastroenterol Hepatol. 2022;20(3):511-524.

Distribution of NASH Inflammatory Activity Grade (Severity) Before and 1 Year After Surgery



Lassailly G, Caiazzo R, Buob D, et al. Gastroenterology. 2015;149(2):379-388.

Distribution of Fibrosis Stage Before and 1 Year After Surgery



Lassailly G, Caiazzo R, Buob D, et al. Gastroenterology. 2015;149(2):379-388.

Bariatric Surgery in Cirrhosis

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- Data regarding hepatic benefits are limited in cirrhosis.
- Focus on striking a balance between desired weight loss and risk of complications, including hepatic decompensation.
- Currently cannot be considered a primary therapy for the treatment of compensated MASH cirrhosis.
- Associated with an increased risk of postoperative mortality.
- Should only be considered at high volume centers under special circumstances such as when combined with liver transplant or as part of a research protocol.

Lassailly G, Caiazzo R, Buob D, et al. Gastroenterology. 2015;149(2):379-388.
Lassailly G, Caiazzo R, Ntandja-Wandji L-C, et al. Gastroenterology. 2020;159(4):1290-1301.
Jirapinyo P, McCarty TR, Dolan RD, et al. Clin Gastroenterol Hepatol. 2022;20(3):511-524.

Summary: Bariatric Surgery

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- Bariatric surgery should be considered as a therapeutic option in patients who meet criteria for metabolic weight loss surgery.
- Resolves MASLD or MASH in the majority of patients without cirrhosis and reduces mortality from CVD and malignancy.
- Decompensated cirrhosis should be considered an absolute contraindication for bariatric surgery.

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS et al. Hepatology. 2023;77(5):1797-1835.

Medications

- There are currently no FDA-approved drugs for the treatment of MASLD at any disease stage.
- However, there are medications approved for other indications that have shown benefits for MASLD in clinical trials and should be considered under specific circumstances.

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS et al. Hepatology. 2023;77(5):1797-1835.

GLP-1 Receptor Agonists (GLP-1RAs)

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- The biological effects of GLP-1RAs on lipids, glucose metabolism, weight loss, and cardiovascular outcomes make them attractive agents for treatment of MASH.
- Some approved for the treatment of diabetes and obesity.
- None have been approved for treatment of MASH.
- Phase 2b randomized controlled trials of daily subcutaneous semaglutide, 320 patients with NASH (F1–F3) were randomized to 0.1, 0.2, or 0.4 mg or placebo daily for 72 weeks.
- Primary endpoint: resolution of NASH without worsening fibrosis.
- MASH resolution was dose-dependent and occurred in 59% in the treatment group versus 17% in the placebo group ($p < 0.001$).

Armstrong MJ, Gaunt P, Aithal GP, et al. Lancet. 2016;387(10019):679-690.
Newsome PN, Buchholtz K, Cusi K, et al. N Engl J Med. 2021;384(12):1113-1124.

Semaglutide

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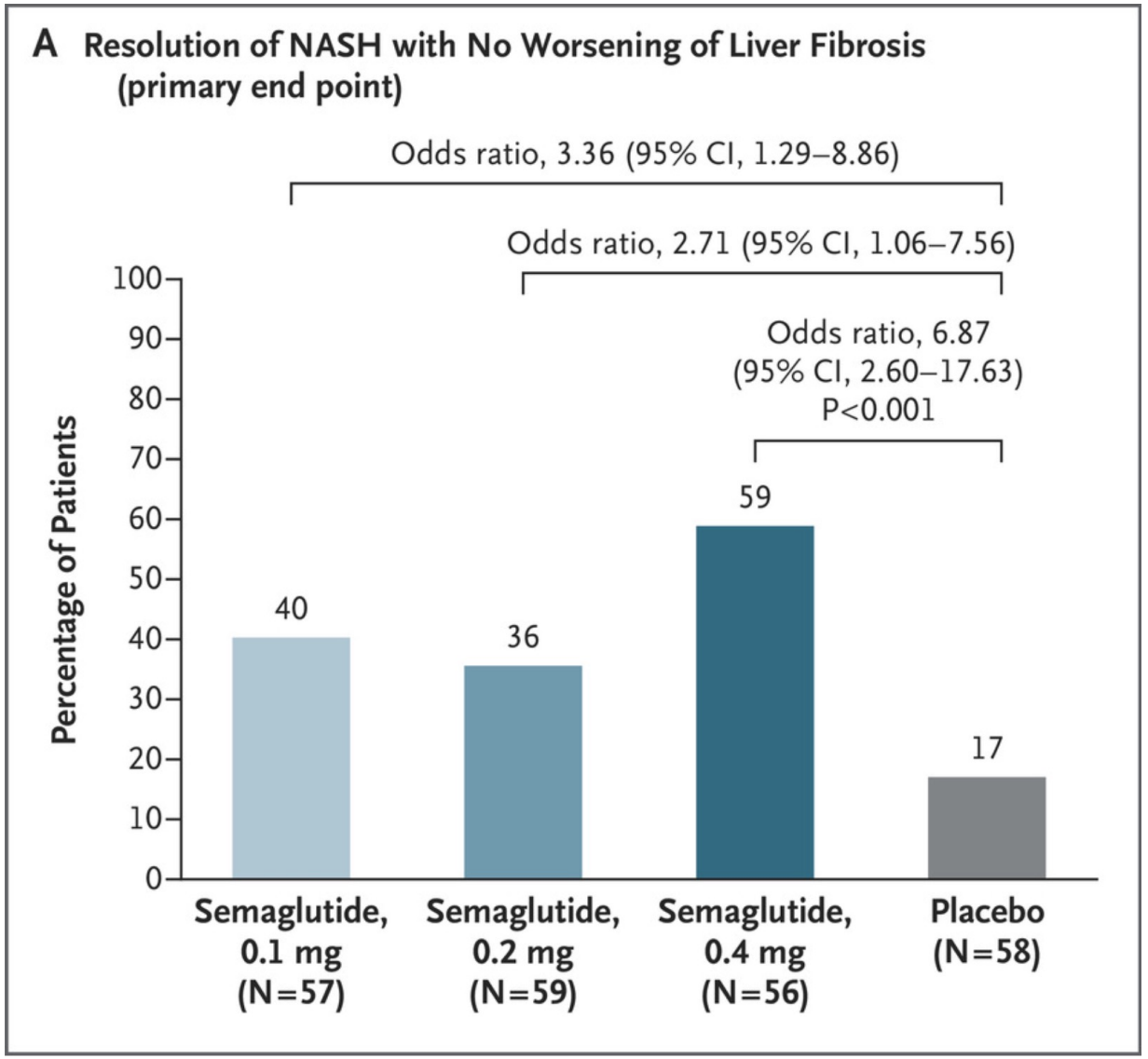
Table 2. Changes between Baseline and Week 72 in Selected Supportive Secondary End Points.*

End Point	Semaglutide 0.1-mg Group (N=80)	Semaglutide 0.2-mg Group (N=78)	Semaglutide 0.4-mg Group (N=82)	Placebo Group (N=80)
Ratio of value at wk 72 to value at baseline				
Alanine aminotransferase	0.63	0.58	0.42	0.81
Aspartate aminotransferase	0.70	0.65	0.52	0.84
Caspase-cleaved cytokeratin-18 fragment M30†	0.55	0.50	0.47	0.78
Caspase-cleaved cytokeratin-18 fragment M65†	0.53	0.52	0.42	0.71
Total cholesterol	0.97	1.00	0.93	0.94
Triglycerides	0.88	0.90	0.73	0.97
Liver stiffness, as assessed by FibroScan‡	0.76	0.71	0.72	1.02
Change from baseline to wk 72				
Enhanced liver fibrosis test score	–0.34	–0.39	–0.56	0.01
Body weight — %	–4.84	–8.91	–12.51	–0.61
Glycated hemoglobin level among patients with type 2 diabetes — percentage points§	–0.63	–1.07	–1.15	–0.01

* Data are from all the patients during the in-trial observation period (from randomization until the last study-related procedure). A lower ratio of the value at week 72 to the value at baseline indicates a larger reduction.
† Higher levels of cytokeratin-18 fragments are a biomarker of hepatocyte apoptosis.
‡ This assessment was performed only at sites at which FibroScan equipment was available. Changes in liver steatosis were assessed in 161 patients, and changes in liver stiffness were assessed in 212 patients.
§ These values were based on the number of patients with type 2 diabetes in each group (49, 51, 49, and 50 patients in the 0.1-mg, 0.2-mg, 0.4-mg, and placebo groups, respectively).

Newsome PN, Buchholtz K, Cusi K, et al. N Engl J Med. 2021;384(12):1113-1124.



Newsome PN, Buchholtz K, Cusi K, et al. N Engl J Med. 2021;384(12):1113-1124.

Summary: Treatment

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- There are currently no FDA-approved medications for the treatment of MASLD.
- Drugs approved to treat associated comorbidities with potential benefit in MASLD may be considered in the appropriate clinical setting.
- Semaglutide can be considered for its approved indications (T2DM/obesity) in patients with MASH.
- Vitamin E can be considered in select individuals as it improves MASH in some patients without diabetes.

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS et al. Hepatology. 2023;77(5):1797-1835.

Future Directions

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- The number of trials in MASLD has increased exponentially over the last 10 years.
- Several therapeutic agents for MASLD are in late-stage development.
- Further validation of biomarkers that predict liver-related outcomes underway.
- Adoption of AI-based technologies will allow more accurate quantification of fibrosis and highlight early signs of treatment response.

Rinella ME, Neuschwander-Tetri BA, Siddiqui MS et al. Hepatology. 2023;77(5):1797-1835.

An Action Agenda for Turning on Fatty Liver Disease

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- 344 experts and practitioners
- 94 countries represented
- Robust Delphi methodology with two rounds of voting
- 29 ranked action priorities across six domains
- A roadmap to drive action at the local, regional, and global levels

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AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HEPATOLOGY

Lazarus JV, Mark HE, Allen AM, et al. Hepatology. 2024;79(2):502-523.

Public Health Framework for Impacting Steatotic Liver Disease (SLD) Incidence and Progression Via Risk Factors

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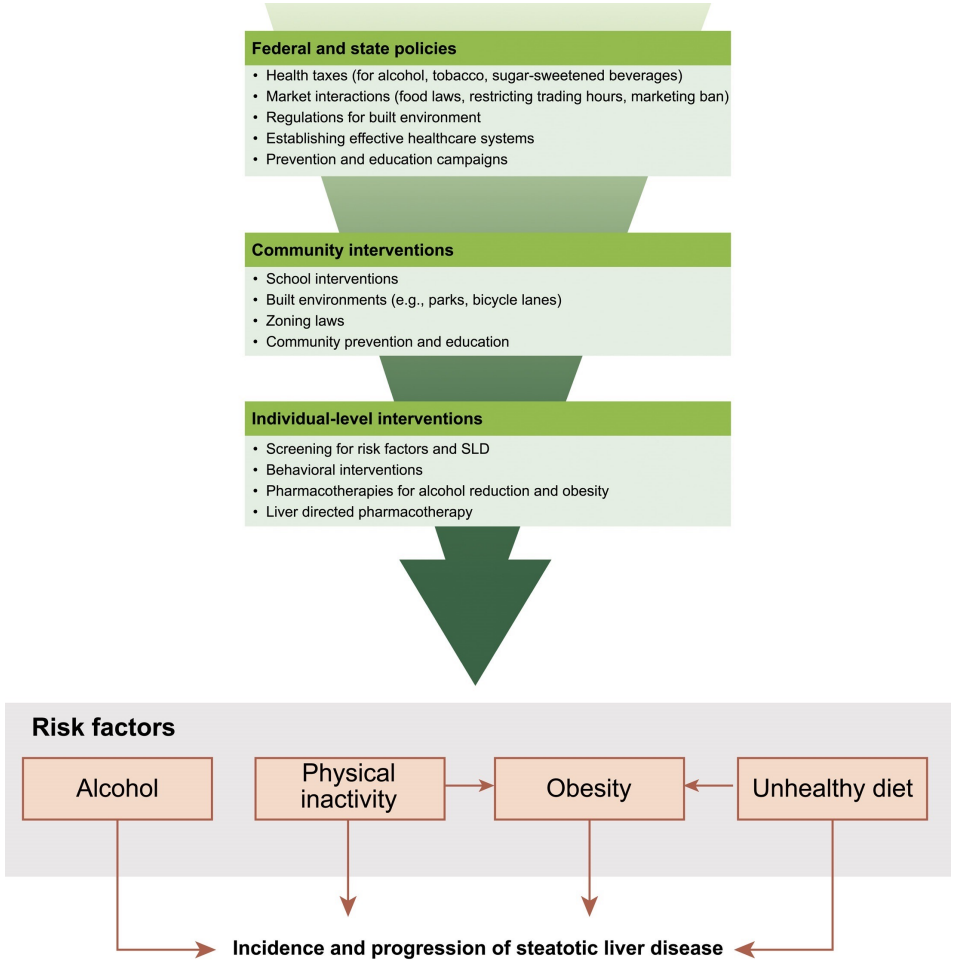

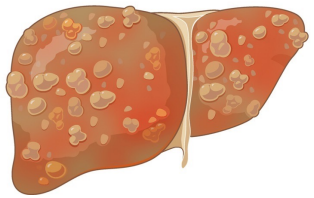

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Balakrishnan M, Rehm J. Hepatology. 2024;79(2):451-459.

Conclusion

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- MASLD is a public health challenge and emergency.
- Requires multidisciplinary and multisectoral responses.
- The rates of fibrosis progression and hepatic decompensation vary depending on baseline disease severity, genetic, individual, environmental, and comorbid disease determinants.
- CVD and nonhepatic malignancies are the most common causes of mortality in patients with MASLD without advanced fibrosis.
- Death from liver disease predominates in patients with advanced fibrosis.
- Early identification of at-risk patients is essential to allow early intervention.

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Audience Question and Answer

Amy Zack, MD

Case Western Reserve University School of Medicine

Cleveland Clinic

Speakers

REMINDER:
Submit questions using the 'Q&A' feature

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Next Steps and Wrap Up

Shari Bolen, MD, MPH
Case Western Reserve University School of Medicine

THANK YOU!

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